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Considerations and challenges for patients with refractory and relapsed acute myeloid leukaemia

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ABSTRACT

Despite advances in understanding the complexities of acute myeloid leukaemia (AML), the treatment of refractory or relapsed AML (rrAML) remains a daunting clinical challenge. Numerous clinical trials have failed to identify new treatments or combinations of existing therapies that substantially improve outcomes and survival. This may be due, at least in part, to heterogeneity among study patients with respect to multiple inter-related factors that have been shown to affect treatment outcomes for patients with rrAML; such factors include age, cytogenetics, immunophenotypic changes, and (in the case of relapsed AML) duration of first complete remission, or if the patient has had a previous blood and marrow transplant (BMT). A clear understanding of disease characteristics and patient-related factors that influence treatment response, as well as expected outcomes with existing and emerging therapies, can aid clinicians in helping their patients navigate through this complex disease state.

Contents

1. Introduction

Acute myeloid leukaemia (AML) is the most common of the acute leukaemias among adults [1], with approximately 20,000 new cases expected in the US in 2015 [2] and an estimated incidence of 18,000 new cases annually in the European Union [3]. AML

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is primarily a disease of older adults; the median age at diagnosis is approximately 67 years [2]. Although survival has generally improved since the 1980s and 1990s, the 5-year relative survival rate still is only about 25% in the US [2] and is 15% to 20% in Europe [3–7].

Induction therapy with intensive chemotherapy regimens can produce a complete remission (CR) in about 50% to ≥80% of adult patients with newly diagnosed AML [8,9]. However, this leaves many patients who do not respond to induction treatment. Also, even among patients who achieve CR, the majority eventually relapse despite receiving post-remission therapy; relapses can occur several months to years after the initial remission, but the risk is highest within the first 3 years after initial treatment [10–12]. Thus, refractory or relapsed AML (rrAML) is a relatively common clinical scenario, but one that is difficult to manage, as effective therapies are limited. Also, rrAML is a very heterogeneous disease in which patient and disease characteristics need to be carefully considered when managing treatment over time.

Overall, patients with rrAML have a poor prognosis and few treatment options, as there currently is no standard of care [8,13]. Challenges in treating patients with rrAML include accurately assessing the disease prognosis and likelihood of achieving CR, selecting the salvage therapy that is most likely to succeed and that can be tolerated, and identifying patients for whom haematopoietic cell transplantation (HCT) is a viable option [14].

The purpose of this manuscript is to discuss the clinical considerations that present challenges in trying to achieve effective treatment of rrAML. In the context of these considerations, current treatment guidelines and emerging treatment options for rrAML in late-stage development are also reviewed. References for this review were identified through searches of PubMed with the search terms "('acute myeloid leukemia' OR "acute myeloid leukaemia" OR "acute myelogenous leukemia" OR "acute myelogenous leukaemia") AND (relaps*[ti] OR refractory [ti]) NOT child*" and were limited to those published in the last 10 years. Articles were also identified through reviews of reference lists from the retrieved articles and treatment guidelines. Only papers published in English were reviewed. The final reference list was generated on the basis of relevance to the scope of this review.

2. Impact of patient characteristics on outcomes in relapsed/refractory acute myeloid leukaemia

Several patient characteristics are relevant in assessing a patient's prognosis and in selecting appropriate treatments for rrAML. Multiple inter-related factors, including age, cytogenetics, immunophenotypic changes, and (in the case of relapsed AML) duration of first CR, have been shown to affect treatment outcomes for patients with rrAML [15–18]. Variability in these characteristics among patient populations in treatment studies may be one reason why clinical trials thus far have failed to identify a single preferred regimen or standard of care [13].

2.1. Age

Age is an important prognostic factor in patients with rrAML, with younger patients generally having a better prognosis than older patients. In AML in general, epidemiological data have shown that survival decreases as age increases, particularly in patients aged ≥65 years [5,6,19]. Considering rrAML specifically, age has been identified as one of several significant predictors of both response to salvage treatment [20] and survival [15,17,20]. For example, the prognostic index for patients aged 15–60 years in first relapse, developed by Breems and colleagues, includes age at relapse (3 strata: ≤35 years, 36–45 years, and >45 years); younger age at relapse was associated with improved survival [15]. Similarly, retrospective analysis by Kurosawa and colleagues found that among patients aged 16–70 years in first relapse, overall survival (OS) was significantly longer for the subgroup of patients aged ≤49 years compared with the subgroup aged ≥50 years ($P < 0.001$); however, age was not identified as an independent prognostic factor in a multivariate analysis [17].

Several characteristics of AML may vary with age and contribute to poor treatment response or survival in older patients. Analysis of several studies by the Southwest Oncology Group (SWOG) found that likelihood of unfavourable cytogenetics increased with age, especially for those >75 years old; the rate of unfavourable cytogenetics was 35% among patients aged <56 years compared with 50% in those aged >75 years, while the incidence rates of favourable cytogenetics were 17% and 4%, respectively ($P < 0.001$ [test for heterogeneity among age groups]) [21]. This study showed that older patients more commonly have AML that expresses multidrug resistance (33% of patients aged <56 years versus 61% to 62% among patients aged 56–75 years, and 57% of patients aged >75 years) and that is resistant to chemotherapy (27% of patients aged <56 years and 36% among those aged >75 years) [21]. Although not specific to refractory or relapsed disease, these characteristics contribute to the challenge in finding effective treatments that can produce CR and improve survival in patients with rrAML, particularly those who are older.

In addition to considerations regarding efficacy, treatment selection for patients with rrAML also must take into consideration age and age-related factors that may affect the intensity of treatment that the patient may be able to tolerate. Treatment guidelines for rrAML (and for newly diagnosed AML) generally use a threshold of 60 years as a therapeutic divergence point and include lower-intensity treatment options for older patients, particularly those older than 75 years and/or who are unlikely to tolerate standard treatment [1,8,22]. However, treatment decisions should not be based on age alone; rather, disease characteristics (e.g., cytogenetic risk) and other relevant patient characteristics should be taken into account [1,8,22].

Age-related factors also can have an impact on the tolerability or toxicity of treatment for older patients with rrAML. For example, older patients have an increased likelihood of the following: comorbid conditions, along with concomitant medications that could contribute to drug-drug interactions; impaired renal or liver function that could decrease drug clearance; reduced immune competence; and poor performance status, particularly following intensive initial treatment [23]. Performance status, creatinine, and albumin were among the variables included in multivariate models for predicting early mortality (at 28, 60, or 90 days) in patients with rrAML recently described by Godwin and colleagues [24].

2.2. Duration of first complete remission

For patients with relapsed AML, duration of first CR (CR1) is widely recognised as an important predictor of outcome after salvage therapy; longer duration of CR1 is associated with better survival [15,17,18,25]. CR rate and disease-free survival (DFS) following salvage therapy decrease continuously as duration of CR1 decreases [26]. In the European Prognostic Index (EPI), risk based on duration of CR1 is stratified into 3 categories: ≤6 months, 7–18 months, or >18 months [15]. A threshold of 12 months is used in some treatment guidelines and prognostic indexes [1,18], as it has been shown that patients whose CR1 lasts longer than 12 months generally have a better prognosis (higher second CR [CR2] rates and longer survival) [20]. In particular, CR1 less than 6 months has been associated with poor survival following salvage therapy (e.g., intensive chemotherapy, HCT, or other treatments) [15,27]. Recent analysis of data from the HOVON/SAKK